



Antimicrobial Resistance Best Practices

Working Group Report and Case Studies

November 2022

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Introduction

The International Coalition of Medicines Regulatory Authorities (ICMRA) is an international executive-level coalition of key regulators from every region in the world. It provides a global strategic focus for medicines regulators and gives strategic leadership on shared regulatory issues and challenges.

Following its mission to safeguard public health, ICMRA adopted antimicrobial resistance (AMR) as a strategic priority and committed its support for the fight against AMR in a joint [statement](#) published in 2019. Globally recognized as one of the greatest threats to public health, AMR is already a significant burden on human health, health care and economies worldwide. AMR does not recognize borders, and with widespread trade and travel, a co-operative and coordinated international response is required to respond to this growing threat.

Building on ICMRA's AMR commitment, a new project on AMR best practices was adopted during the ICMRA Plenary Meeting in April 2021. Leveraging collective knowledge and experience, the project aimed to develop short case studies to highlight some of the successful or promising regulatory and non-regulatory interventions that are used in different jurisdictions to address AMR. A Working Group was convened by Health Canada in September 2021 to advance the project. Working group members are listed in Annex 1.

This report presents the resulting case studies. These examples are intended to serve as tools to raise awareness, within our own membership and beyond, of some of the important, promising actions taken to date to combat AMR. These may promote further discussions within our membership, strengthening our resolve to take bold steps to address this important public health issue and setting the stage for future collaborations. It may also be possible to adapt these best practices for implementation across member countries.

We all have a role to play in combatting AMR. ICMRA recognizes that AMR is a complex, multi-faceted problem, and is calling for a coordinated, One Health response across all sectors, including public health, animal health, and the environment. A concerted and collaborative effort from all partners is essential to ensuring our success in addressing this threat to our health, economies and security. Lives around the world depend on it.

Case Study Topics

Recognizing the importance of a holistic and multisectoral approach to address the growing threat of AMR, the case studies are intended to capture a range of practices across the One Health spectrum, including addressing antimicrobial resistance and use (AMR/AMU) in humans, animals, food, and the environment. Most case studies relate to the regulation of medicines for human health given the ICMRA orientation, however, linkages with other One Health areas are also highlighted to promote collaboration within and across national and international organizations across sectors to combat AMR. Below is a brief introduction to each case study, which were developed by ICMRA colleagues and partners. Complete case studies are found in Annex 2.

1. Regulatory flexibilities that aid in successfully bringing novel therapies to market

Lead: Biomedical Advanced Research and Development Authority (USA)

In the context of AMR, the Biomedical Advanced Research and Development Authority (BARDA) in the United States drives innovation and promotes the development of novel antimicrobial therapies together with industry partners by providing funding and subject matter expertise to offset high research and development costs and technical risk. The standard approach to developing supporting data packages required for regulatory review is not always applicable for certain non-traditional therapies. The insights from this case study provide awareness to the regulators on BARDA model and best regulatory practices for coordination and collaborative efforts related to the development and availability of MCMs in public health medical emergencies.

2. Sales reporting of medically important antimicrobials for veterinary use informs antimicrobial resistance/antimicrobial use surveillance and stewardship initiatives

Lead: Health Canada in collaboration with the Public Health Agency of Canada

For over a decade, voluntarily reported sales data has shown that a significant volume of antimicrobials were intended for use in food-producing animals in Canada. Several classes of antimicrobials used in animals are also used in humans and some are essential for treating serious, life-threatening infections. The importance of this group of drugs to human medicine reinforces the necessity of promoting responsible use initiatives in the animal sector to limit the selection pressure for the development and spread of resistant pathogens in both animals and humans. As of 2018, Canada mandated the reporting of annual sales volumes of medically important antimicrobials (those important to human medicine¹) for intended use in animals. This case study presents the Veterinary Antimicrobial Sales Reporting (VASR) system, a joint effort between the Public Health Agency of Canada and Health Canada that collects data on the total quantity of antimicrobials sold or compounded by animal species, and by province/territory, to support AMR/AMU surveillance and stewardship efforts to reduce AMU in

¹ <https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html>

animals. This case study will outline the parameters for sales reporting in VASR, including the utility of the sales data to inform targeted evidence-based actions to slow AMR.

3. Lessons learned from the regulatory agilities implemented in response to the COVID-19 pandemic

Lead: Health Canada in consultation with the European Medicines Agency

The COVID-19 pandemic created an unprecedented urgent need for access to health products in an expedited manner that was not feasible within existing regulatory frameworks. In response, international medicines regulators adapted to the pressure with regulatory flexibilities to meet the emerging and critical demands of the COVID-19 pandemic. The purpose of this case study is to describe the regulatory agilities implemented in response to the COVID-19 pandemic from the Canadian perspective. The measures that Health Canada and its partners supported and continue to support promote the safe and timely access to critical COVID-19 health products through temporary legislative, regulatory and policy measures and partnerships with international regulatory bodies like the European Medicines Agency. Given that AMR is a public health threat that, if left unchecked, may cause the next pandemic, it is important to consider how the lessons learned from regulatory agilities implemented in response to the COVID-19 pandemic can be applied to combat AMR.

4. Restricting the sale and supply of non-prescription availability of antibiotics

Lead: Medicines and Healthcare products Regulatory Agency (United Kingdom)

When tackling AMR, it is vital not to overlook the non-prescription availability and supply of antibiotic-containing compounds. This availability and supply should be monitored and updated to ensure that it remains clinically relevant and accurately reflects any updates to clinical guidance. This case study, focusing on tyrothricin-containing lozenges, aims to provide an example of restricting the sale/ supply of non-prescription antibiotic-containing compounds, considering updated clinical guidance on the treatment of acute sore throat.

5. Development and progress of a pilot study on reimbursement models for novel antimicrobials

Lead: Public Health Agency of Sweden

The antimicrobial market failure presents a major challenge in our ability to combat AMR and this issue has been receiving increased international attention, with some jurisdictions exploring ways to create the right economic conditions to address some of their most urgent needs. In addition to global market failure, in Sweden, problems additionally arise when new products are not launched onto the Swedish market and when existing products are withdrawn. In response to these problems the Public Health Agency of Sweden has proposed a pilot study of an alternative reimbursement model to gain and keep access to antibiotics available on the Swedish market. This case study describes the design and implementation of the novel reimbursement model for antibiotics being piloted in Sweden.

6. Reporting selective antibiograms to inform antimicrobial choice

Lead: Swedish Medical Products Agency

An antibiogram provides a snapshot in time of the susceptibility of bacterial isolates to various antimicrobial drugs. Clinicians use antibiograms to guide their antimicrobial prescribing and support them in selecting the best available option and ideally a narrow-spectrum antibiotic, if possible. This case study explains the use and selective reporting of antibiograms of urinary cultures for Enterobacteriaceae from patients with symptoms of cystitis and describes how resulting prescription rates of certain antibiotics changed over time.

7. Feedback on prescriber data for antibiotics

Lead: Swedish Medical Products Agency

Providing feedback to prescribers on their antibiotic prescribing practices is a powerful and effective way to influence antibiotic prescription habits. This case study describes the methods implemented in Sweden to provide feedback on prescriber data for antibiotics. This feedback is leveraged as an opportunity to inform, educate and correct misperceptions on antibiotic prescribing. Feedback provided to prescribers includes data at the regional, hospital and health centre level as well as at the individual level.

8. Treatment recommendations for common infections in outpatient care – the Rainbow Pamphlet

Lead: Swedish Medical Products Agency

The need to reduce inappropriate use of antimicrobials is an urgent element of the actions to address increasing AMR. This case study describes Sweden's Rainbow Pamphlet, an informational resource launched by the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA in Swedish) in 2010. The Rainbow Pamphlet provides fulsome, update to date, accessible and concise information on the treatment recommendations for common infections in outpatient care. This resource is available as a paper pamphlet or through the STRAMA mobile application and its dissemination supported by communications targeted at healthcare professionals and the public.

9. Developing methods for monitoring AMR in the environment

Lead: Swedish Medical Products Agency

A One Health approach promotes harmonised surveillance across human, veterinary and food sectors, and the use of common outcome indicators to monitor AMR and AMU. To date, several joint national or international reports publish AMR trends for key indicator bacteria and key antibiotics. However, there is no clear consensus on which indicators to measure for the environmental sector. This case study describes two projects in Sweden, Project EMBARK (Establishing a Monitoring Baseline for Antimicrobial Resistance in Key environments) and Antibiotikasmart Sverige (Antibiotic Smart Sweden), that have been undertaken to develop methods for monitoring AMR in the environment.

Next Steps

The ICMRA membership is invited to leverage the case studies found in this report to increase awareness on best practices to respond to AMR and to consider whether these may be adapted for implementation in their national context. This report may also be shared with public health agency counterparts and with colleagues from other One Health areas in order to inspire national action.

Annex 1: Working Group Members

- Health Canada (HC); Canada – Project Lead
- European Medicines Agency (EMA); European Union
- Medicines and Healthcare products Regulatory Agency (MHRA); United Kingdom
- Ministry of Health, Labour and Welfare (MHLW); Japan
- National Administration of Drugs, Food and Medical Devices (ANMAT), Argentina
- National Agency for Food and Drug Administration and Control (NAFDAC); Nigeria
- Saudi Food & Drug Authority (SFDA); Saudi Arabia
- Swedish Medical Products Agency (SMPA); Sweden

Annex 2: Case Studies

Flexibilities to successfully bring novel therapies to market

Lead: Biomedical Advanced Research and Development Authority

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| Theme | Human medicines |
| Region / Agency | United States Department of Health and Human Services (DHHS) Assistance Secretary for Emergency Preparedness and Response (ASPR) Biomedical Advanced Research and Development Agency (BARDA) |
| Problem / Challenge | <p>BARDA’s mission in the antibacterial space is to reduce the morbidity and mortality caused by drug resistant infections following a public health emergency as well as biothreat pathogens. Our goal is to accelerate the development of therapeutics and diagnostics to enable clinicians and first responders to prevent, diagnose, and treat biological threat agent infections, antibiotic-resistant secondary infections, and hospital-associated and community-acquired infections. BARDA accomplishes this by establishing innovative public-private partnerships with pharmaceutical companies and biotech companies working in the antimicrobial space. Through these partnerships we provide non-dilutive funding and subject matter expertise. This support, both financial and technical offsets the high research and development (R&D) costs and reduces R&D risk.</p> <p>BARDA works with its industry partners throughout the development process with the goal that these antimicrobials receive marketing approval from the Food and Drug Administration (FDA) and thus are available to physicians to prevent and treat antibiotic-resistant secondary bacterial infections and bioterrorism infections. BARDA solicits proposals from product developers to co-support the advanced research and development of their candidate products under the BARDA Broad Agency Announcement (BAA) and anticipates these activities will serve to advance candidate medical countermeasures (MCMs) toward licensure or approval by FDA. Once an award is signed, the contractor begins to work on the plan contained within the contract to meet all milestones and deliverables.</p> |
| Solution / Intervention | <p>Awards resulting from the BARDA BAA may also benefit from BARDA’s core services that include an animal study network; flexible manufacturing facilities; and technical expertise in development, manufacturing, regulatory affairs, quality systems, and clinical study design. A sound regulatory master plan is critical to successfully bring products to market and should outline the activities necessary to obtain FDA approval, licensure, and clearance of the product.</p> <p>The plan should cover the crucial development pathway, integrating all products, risk evaluation, and mitigation at all development stages; non-clinical and clinical testing; and manufacturing activities using the most current and available information, including documented and time-relevant</p> |

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| | <p>consultation with FDA. The plan should also include a tentative schedule for regulatory milestones.</p> <p>One of the best practices that the Regulatory and Quality Affairs (RQA) Division has been utilizing is a Memorandum of Understanding (MOU) with FDA. FDA and ASPR/BARDA signed an MOU to provide a framework for coordination and collaborative efforts related to the development and availability of MCMs in public health medical emergencies. The discussions are kept on scientific or regulatory issues within FDA’s areas of responsibility and expertise and provide a forum for a mutual exchange of opinions and ideas. BARDA ensures that the discussions avoid any appearance that procurement, contracting, or investment considerations may influence FDA regulatory decision-making concerning product approval or authorization.</p> |
| Results / Accomplishments | RQA facilitated multiple key meetings under the MOU related to the regulatory strategy and development for our portfolio of antimicrobials and products that target both MDR pathogens and bioterrorism infections. These interactions have resulted in clear and successful regulatory strategies vetted by FDA and important feedback/concurrence on study designs. |
| Learnings / Recommendations | <ul style="list-style-type: none"> • Clear acquisition process that provides not only financial but also technical support • Sound regulatory plan • Memorandum of Understanding (MOU) with regulatory agency to provide a framework for coordination and collaborative efforts related to the development and availability of MCMs in public health medical emergencies |
| Infographic and/or web links | <ul style="list-style-type: none"> • https://www.phe.gov/about/amcg/BARDA-BAA/Pages/default.aspx • https://www.fda.gov/about-fda/domestic-mous/mou-225-19-013 |

Sales reporting of medically important antimicrobials for veterinary use informs antimicrobial resistance/antimicrobial use surveillance and stewardship initiatives

Lead: Health Canada

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| Theme | Veterinary medicine |
| Region / Agency | Canada Health Canada, Health Products and Food Branch, Veterinary Drugs Directorate and the Public Health Agency of Canada (PHAC) |
| Problem / Challenge | <p>AMR is a global public health issue of increasing concern. Anytime antimicrobials are used, they can contribute to the emergence and spread of resistant bacteria. The inappropriate use of antimicrobials in people, animals and plants is escalating the AMR problem. To reduce the need for and use of antimicrobials in food producing animals, a multi-pronged approach is necessary focused on surveillance, infection prevention, biosecurity and access to alternative health products to keep animals healthy.</p> <p>Voluntary industry reported data for over a decade have shown that a significant volume of antimicrobials are distributed for use in food-producing animals in Canada. To support antimicrobial use and resistance surveillance and responsible use initiatives, comprehensive and timely surveillance information is needed to assess the antimicrobials available and intended for use in animals, focused on those important in human medicine.</p> |
| Solution / Intervention | <p>Regulatory changes to Canada's <i>Food and Drug Regulations</i> were made in 2017 to strengthen oversight of antimicrobials available for use in animals to obtain data on antimicrobials available for sale in Canada. These changes require manufacturers, importers and compounders to report annual sales of medically important antimicrobials intended for use in animals (those important to human medicine; as outlined on List A: List of Certain Antimicrobial Active Pharmaceutical Ingredients). Prior to these changes, antimicrobial distribution data were provided voluntarily by the veterinary drug industry association (the Canadian Animal Health Institute) to PHAC, through the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS).</p> <p>To implement the regulatory reporting requirements, Health Canada and PHAC developed the Veterinary Antimicrobial Sales Reporting (VASR) system. This information helps to:</p> <ul style="list-style-type: none"> • provide a better understanding of the quantity of antimicrobials available for use in animals; • support surveillance, including interpretation of patterns and trends in AMR; and • provide relevant information that could help assess the impact on human health from the use of specific antimicrobials in animals. <p>Sales reports of veterinary drugs containing active pharmaceutical ingredients (APIs) on List A must include:</p> |

- the total quantity sold or compounded
- the approximate quantity sold or compounded for each intended animal species

Sales reports are required to be submitted every year and to reflect data collected over the period of January 1 to December 31. The annual deadline to submit sales reports of the previous calendar year to Health Canada is March 31 of each year.

Health Canada’s [Veterinary Drugs Directorate](#) is responsible for collecting the required data, managing the VASR system and initial screening of these data for accuracy and completeness. PHAC’s [CIPARS](#) is responsible for the validation, analysis and reporting of these results and PHAC also provides the innovative platform, the [Canadian Network for Public Health Intelligence](#) (CNPHI).

The VASR platform provides an integrated notification system, optimizes data entry for the user through the accessible web based interface, and enhances surveillance capabilities for PHAC and HC through purpose-built analytics, custom querying, and generation of preliminary dashboard statistics.

The sales data can inform stewardship activities through direct communication of findings, but also through integration with information arising from surveillance of antimicrobial use practices on-farm, surveillance of farm biosecurity and management practices, surveillance of diseases on farm, and AMR surveillance data throughout the food chain.

Engagement with agri-food stakeholders are instrumental to ensure the sector-specific data is communicated in a timely manner across producer groups (e.g., cattle, poultry, and swine) and other relevant stakeholders to enhance the prudent use of these important drugs and preserve their effectiveness in human and veterinary medicine.

**Results /
Accomplishments**

Regulatory guidance or changes

- Amendments to Canada’s [Food and Drug Regulations](#) were published in the Canada Gazette, Part II on May 17, 2017. These changes aim to increase oversight of antimicrobials available for use in animals and include the regulatory requirement for manufacturers, importers, and compounders to report total quantity sold or compounded and approximate quantity sold or compounded for each intended animal species annually, through the web-based VASR platform.
 - The following persons submit sales reports for veterinary drugs containing APIs set out on [List A: List of Certain Antimicrobial Active Pharmaceutical Ingredients](#):
 - *Importers*: anyone importing such a drug into Canada for sale
 - *Manufacturers*: anyone who sells such a drug in Canada under their own trade name or mark controlled by them
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| | <ul style="list-style-type: none"> • <i>Compounders</i>: anyone (for example a veterinarian or pharmacist) who compounds a product for veterinary use using antimicrobial ingredients on List A that are sourced as (i.e. meaning any of the following inputs into the final compounded product): <ul style="list-style-type: none"> ○ an API set out on List A (such as the raw ingredient) ○ a human drug in dosage form (e.g. products with a drug identification number - DIN) containing an API set out on List A ○ a veterinary drug in dosage form (e.g. products with a DIN) containing an API set out on List A, in particular when compounded for food-producing animals <p><i>Metrics / statistics related to measuring or evaluating the intervention</i></p> <p><u>Metrics to report the sales data</u></p> <ul style="list-style-type: none"> • Total quantity (kg) and the total kg adjusted by animal biomass sold over time as reported by the VASR system captured for manufacturers and importers for medically important antimicrobials <p><u>Metrics to evaluate surveillance system</u></p> <ul style="list-style-type: none"> • The number of manufacturers and importers reporting sales to the system who either manufacture List A API's or import such a drug into Canada for sale. • Communication of the data to stakeholder groups (e.g., presentations to commodity groups, # reports, presentation to WAAW) • Uptake of information from the surveillance program (e.g., stakeholder groups considering voluntary target setting for reductions) |
| <p>Learnings / Recommendations</p> | <ul style="list-style-type: none"> • To continue collecting sales information, annually from importers, compounders and manufacturers on sales of medically important antimicrobials intended for use in animals to support antimicrobial use and resistance surveillance and stewardship initiatives. <p><i>Next steps / plans for future</i></p> <ul style="list-style-type: none"> • Targeted communications of the sales data to inform industry-led activities to support the prudent use of antimicrobials, including the need for and use of antimicrobials in the agri-food sector. This includes supporting a multi-pronged approach to animal health and wellness (such as IPAC, biosecurity measures, vaccines, animal husbandry practices and alternative health products). |
| <p>Infographic and/or web links</p> | <ul style="list-style-type: none"> • Enhancing antimicrobial stewardship by strengthening the veterinary drug regulatory framework: https://pubmed.ncbi.nlm.nih.gov/29770050/ • About Veterinary Antimicrobial Sales Reporting (VASR) system: https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/veterinary-antimicrobial-sales-reporting.html • Annual Highlights Reports (located on above webpage), direct links to: <ul style="list-style-type: none"> ○ 2018 ○ 2019 ○ 2020 |

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- Antimicrobial resistance and animals – Actions:
<https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/actions.html#a6>
 - CIPARS 2019 Tables and Figures:
<https://publications.gc.ca/site/eng/9.905145/publication.html>
 - CIPARS 2019 Integrated Findings:
<https://publications.gc.ca/site/eng/9.905141/publication.html>
 - CIPARS Key Findings:
<https://publications.gc.ca/site/eng/9.905137/publication.html>
 - CARSS Report: <https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-report-2021.html#a8>
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Lessons learned from the regulatory agilities implemented in response to the COVID-19 pandemic

Lead: Health Canada in consultation with the European Medicines Agency

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| Theme | Human medicines; Diagnostics tests; Vaccines and other alternatives |
| Region / Agency | Canada and international partners Health Canada in consultation with the European Medicines Agency |
| Problem / Challenge | <p>The COVID-19 pandemic created an unprecedented urgent need for access to health products in an expedited manner that was not feasible within existing regulatory frameworks. In response, international medicines regulators adapted to the pressure with regulatory flexibilities to meet the emerging and critical demands of the COVID-19 pandemic.</p> <p>AMR is a public health threat and if left unchecked, may cause the next pandemic. The purpose of this case study is to describe the regulatory agilities implemented in response to the COVID-19 pandemic from the Canadian perspective to inform the consideration of their applicability to AMR in the future.</p> |
| Solution / Intervention | <p>As part of the government's broad response to the pandemic, Health Canada as Canada's federal health product regulator, introduced innovative and agile regulatory measures. These measures are helping to make health products and medical supplies needed for COVID-19 available to Canadians and health care workers. These measures expedited the regulatory review of COVID-19 health products without compromising safety, efficacy and quality standards and introduced regulatory flexibilities to help maintain supply to these critical supplies.</p> <p>The measures that Health Canada supported and continues to support promote the safe and timely access to critical COVID-19 health products through temporary legislative, regulatory and policy measures and partnerships with international regulatory bodies.</p> <p><u>Temporary legislative, regulatory and policy measures</u></p> <p><i>Drug and vaccine authorization</i></p> <p>On September 16, 2020, Canada's Minister of Health signed the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 (ISAD IO) that introduced a temporary regulatory pathway to help expedite authorizations for COVID-19-related drugs and vaccines without compromising patient safety. The interim order created a more agile pathway to facilitate the availability of COVID-19-related drugs and vaccines for Canadians in 4 ways:</p> <ol style="list-style-type: none"> 1. authorizing a brand new drug based on available evidence with more agile administrative and application requirements 2. authorizing a new drug based on the approval of a trusted foreign regulatory authority |

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3. allowing expanded use of an already approved drug to include COVID-19-related indications based on known evidence with or without an application from the market authorization holder
 4. permitting the Public Health Agency of Canada to import promising COVID-19 drugs for placement (pre-positioning) in Canadian facilities before they are authorized in Canada

As of October 2020, Health Canada began receiving [submissions for approval](#) under the ISAD IO. The data provided in a submission was carefully reviewed to ensure that any new vaccine or treatment made available to Canadians is safe, effective and of high quality.

The ISAD IO expired on September 16, 2021. To ensure that COVID-19-related drugs authorized under the ISAD IO may continue to be imported and sold in Canada, [transition measures](#) were introduced to amend the *Food and Drug Regulations*. The amendments ensure that the [review, authorization and oversight of COVID-19 drugs](#), including new drugs, can now be conducted under the *Regulations*.

Procurement Strategy

Early in its response to the COVID-19 pandemic, the Government of Canada adopted a procurement strategy to secure access to safe and effective COVID-19 vaccines, treatments, diagnostic tests and related supplies. Similar to many other countries, Canada built its COVID-19 health product portfolio in part through advanced purchasing agreements (APAs). APAs are arranged between purchasers and manufacturers that provide upfront financing and/or guarantee of purchase of products that are still under development. The benefit of an APA for manufacturers is that it provides a known return on investment that can allow for accelerated research and development of the product at a lower risk, whereas, for purchasers, it secures their access to the products. APAs have the obligations of a contract, but are more flexible in structure. This flexibility was needed given the uncertainties around when new products would ultimately be developed and receive regulatory authorization.

For example, [Canada built its vaccine portfolio](#) through APAs with seven different pharmaceutical companies in order to secure fast access to vaccines for Canadians. Each company had its own negotiating strategy with different demands and pricing per dose depending on the investments made in research, manufacturing and supply logistics, which added to the complexity of landing agreements. As a common element, all agreements required initial investments with the vaccine manufacturers to support vaccine development, testing and at-risk manufacturing. While waiting for the regulatory authorization of vaccines, Canada began to put in place contracts for the logistics, storage and distribution networks that would be needed once the vaccines were authorized and ready for distribution.

The APA procurement strategy was effective in providing timely access to safe and effective COVID-19 vaccines and has also been used to secure access to COVID-19 treatments and diagnostic test.

Clinical Trials

On May 23, 2020, Canada's Minister of Health signed *Interim Order No. 1 Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19* (CT-IO) that introduced a temporary regulatory pathway for to facilitate clinical trials for potential COVID-19 drugs and medical devices. The CT-IO provided a more efficient and flexible optional pathway for clinical trials related to COVID-19 to meet an urgent public health need by:

- reducing the administrative burden of certain requirements stratified according to the risk of the product;
- facilitating a broader range of trial designs, including larger trials to provide the necessary evidence needed to help confirm a therapy's effectiveness, safety and quality;
- introducing flexibilities for who can conduct a trial as a Qualified Investigator;
- allowing for the application of Terms and Conditions to a clinical trial authorization at any time during the trial;
- introducing flexibilities for obtaining informed consent remotely; and
- allowing for proportionate oversight over the lifecycle of a trial by bringing into force the section of the *Food and Drugs Act* that prohibits the conduct of a clinical trial unless the person holds an authorization to do so in order to enable flexibilities and oversight abilities in this pathway.

The new [Clinical Trials for Medical Devices and Drugs Relating to COVID-19 Regulations](#), published in the Canada Gazette II on March 2, 2022, came into effect on February 27, 2022, following the repeal of the [Interim Order No. 2](#). These regulations will maintain the flexibilities and pathway set out by the interim order until the framework established through the [Clinical Trials Modernization Initiative](#) is in place.

Drug Establishment Licensing (DEL) and Good Manufacturing Practices (GMP)

Health Canada also introduced a number of regulatory flexibilities related to Drug Establishment Licensing (DEL) and Good Manufacturing Practices (GMP) in response to challenges created by the global pandemic, and to safeguard the timely access to high quality drug products for Canadians.

The DEL and GMP regulatory flexibilities related to licensing and inspection of health products include:

1. Foreign Evidence
 - Extension to foreign New Evidence Required By Date (NERBY)
 - Accepting corporate/consultant audit reports to demonstrate GMP compliance of foreign buildings

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- Extension of foreign evidence validity period
2. Domestic Manufacturing
 - Using atypical active pharmaceutical ingredients for domestic manufacturing of sanitizers and disinfectants
 3. Confirmatory and ID Testing
 - Deferring confirmatory testing requirements
 - Modified identity testing
 4. Quality Risk Management
 - Deferring low-risk investigations
 - Using electronic systems that are not fully validated

Partnerships with international regulatory bodies

Health Canada worked and continues to work with international partners on a coordinated and well-aligned approach to the COVID-19 pandemic to ensure that health products are safe, effective and quickly available to Canadians. Collaboration also helps advance the development of diagnostics, treatments and vaccines that will save lives and protect the health and safety of people everywhere. Specifically, our international engagement involves discussing, collaborating and leveraging resources on issues related to:

- clinical trials and investigational testing
- drug and medical device market authorizations
- health product risk assessments
- potential drug and medical device shortages

Such partnerships with international regulators include through the ICMRA, the [Access Consortium](#), multilateral COVID-19 'cluster' meetings, International Post-Market Surveillance Group, Medical Dictionary for Regulatory Activities (MedDRA) management committee, international medical device regulators and by participating in efforts through the WHO and Pan-American Health Organization (PAHO). The European Medicines Agency (EMA) Open pilot initiative was chosen as the featured example of international collaboration for this case study, given it was initiated in response to the COVID-19 pandemic and offers potential applicability to the AMR space.

EMA Open Pilot

The objective of the EMA Open pilot initiative is to allow active international participation of non-EU regulators in the EMA's scientific evaluation of COVID-19 vaccines and therapeutics in the context of the pandemic by regulatory authorities with confidentiality arrangements. The pilot aims to foster better understanding of regulatory outcomes in the face of common challenges, while retaining scientific and regulatory independence of the participating authorities. It also promotes transparency and contributes to public trust in the vaccines and therapeutics.

The EMA invited regulators from Australia, Canada, Japan, Switzerland and the World Health Organization (WHO) to participate in the pilot under the terms of

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| | <p>existing <u>confidentiality arrangements</u>. International collaboration facilitates patient access through harmonisation or convergence, brings additional scientific expertise to a regulatory authority and simplification for pharmaceutical industry. It also increases overall transparency and can contribute to public trust because regulatory decisions are open to peer-review, either formal or informal.</p> <p>This initiative is in line with the principle of reliance and global regulatory good practices. Participation of non-EU regulatory authorities, or selected international organisations, may support the accelerated development and assessment of medicines in the context of COVID-19, where the needs and potentials treatments and vaccines are the same globally. Participation of non-EU regulators can bring additional expertise at a time where workload demands are high due to the pandemic. This active participation can also benefit the non-EU countries, including the possibility to receive applications earlier, to speed up their own assessments and make COVID-19 medicines available to the public faster. International collaboration may increase public trust in procedures and approvals, at a time when vaccine hesitancy has increased.</p> |
| <p>Results / Accomplishments</p> | <p>Metrics measuring success of best practice:</p> <ul style="list-style-type: none"> • As of June 8, 2022, 6 treatments and 7 vaccines were authorized for COVID-19 via these pathways • Between May 2020 and March 2022, a total of 38 clinical trials were authorized under the Interim Orders <p>Outcomes of best practice:</p> <ul style="list-style-type: none"> • Strengthened collaboration and enhanced relationships between international regulators which resulted in: <ul style="list-style-type: none"> ○ Reduced duplication of effort ○ Reduced regulatory burden for industry ○ Significantly reduced review timelines ○ Timely access to vaccines, therapeutics and diagnostic devices |
| <p>Learnings / Recommendations</p> | <p>Health Canada is reviewing these flexibilities, taking into account several considerations including current context and stakeholder feedback, to determine if they should continue, end or be retained with revisions for COVID-19.</p> <p>Health Canada is taking under consideration the lessons learned and stakeholder feedback from these temporary measures put in place for the COVID-19 pandemic in its broader regulatory innovation agenda, which includes five pillars:</p> <ol style="list-style-type: none"> 1. Modernizing clinical trial regulations 2. Enabling advanced therapeutic products 3. Agile licensing for drugs 4. Agile licensing for medical devices 5. Information to Canadians mobile strategy |

The lessons learned that are recommended to be considered as part of the regulatory strategy to address AMR moving forward include:

- Enhanced regulatory flexibility for drugs that address an urgent public health need, e.g., one caused by a drug resistant pathogen
 - Continuing information sharing and regulatory collaboration to strengthen confidence and regulatory decision making to address emerging infectious diseases
 - Promoting the simultaneous filing of submissions in multiple jurisdictions to decrease regulatory burden and earlier access to innovative products
 - Although not a regulatory strategy but rather a procurement strategy, APAs may serve as an effective pull incentive to industry to secure access to novel products
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Non-prescription availability of antibiotics

Lead: Medicines and Healthcare products Regulatory Agency

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| Theme | Human medicines |
| Region / Agency | United Kingdom The Medicines and Healthcare products Regulatory Agency (MHRA) |
| Problem / Challenge | <p>Tyrothricin-containing lozenges, marketed as “Tyrozets” and “Boots Anaesthetic & Antibiotic Throat Lozenges”, have been licensed in the UK as medicines available for purchase at pharmacies since 1968. Alongside tyrothricin, the product contained benzocaine, a local anaesthetic. The indication for Tyrozets was previously “minor mouth and throat irritations”, whilst the Boots Anesthetic and Antibiotic Throat Lozenges were indicated for the relief of sore throats.</p> <p>In April 2018, the National Health Service (NHS) England, issued updated guidance on the treatment of acute sore throat. This guidance advised that prescriptions for the treatment of acute sore throats should not be routinely offered in primary care, as sore throats are self-limiting: clearing up on their own without the need for treatment. Additionally, it was found that most sore throats were caused by a viral infection (rather than bacterial causes). Tyrothricin-containing lozenges were subsequently products that were considered ‘restricted for prescribing’.</p> <p>Following the updated guidance, clinical practice needed to be updated to reflect the fact that tyrothricin lozenges became inappropriate for use in both self-care and primary care.</p> <p>In July 2018, this was brought to the attention of the MHRA, by the Department of Health and Social Care’s Chief Medical Officer (CMO). This communication reflected the advice from the Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI), who stated that the use of tyrothricin-containing lozenges was unjustified, recommending instead that a responsible and prudent use of antibiotics was in the best interest of patient health.</p> |
| Solution / Intervention | <p>The MHRA team investigated the issue, with the aim of reporting back to the Department of Health and Social Care on the feasibility of removing the tyrothricin lozenges from the market, in the interests of protecting public health, and preserving antibiotics for future generations.</p> <p>The MHRA wrote a paper, in July 2018, seeking advice from the United Kingdom’s Commission on Human Medicines (CHM), on the feasibility of removing these products from the market.</p> <p>The matter was considered by the CHM, who took the view that the presence of an antibiotic in an over-the-counter throat lozenge was principally no longer clinically relevant. Additionally, this product could deliver mixed messages to healthcare professionals and the public alike, on appropriate and responsible use of antibiotics.</p> |

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| | <p>The MHRA team wrote out to Marketing Authorisation Holders (MAHs), and a meeting was held with these stakeholders in December 2018, where the MHRA presented the CHM's opinion.</p> <p>The MHRA presented MAHs with numerous alternative regulatory options, including the following: reformulation of the product by removing the tyrothricin (with the option of replacing the tyrothricin with an alternative ingredient, such as an antiseptic), or keeping the existing formula but reclassifying the medicine to a Prescription Only Medicine (POM).</p> |
| <p>Results / Accomplishments</p> | <p>As a result of positive MHRA/ MAH interactions, timely solutions with clear regulatory actions and timelines were agreed. Since the MAH actions were voluntary, it was felt that wider public communications were not required.</p> <p>With regards to MAH plans to submit a marketing authorisation for a potential benzocaine-only product, up-to-date advice was provided to the MAH, on the requirements for different legal product classifications.</p> <p>A final manufacturing date of August 2019, and a sell-through period through to early 2020 was agreed, considering rate of sales, existing stock, and forward planning around the UK exit from the EU.</p> <p>Tyrozets were discontinued in 2020. The discontinuation reflected the updated clinical guidance for acute sore throat treatment.</p> |
| <p>Learnings / Recommendations</p> | <p>Primarily, this case has highlighted the national importance of AMR, as the national licences were brought to the attention of the Chief Medical Officer by the Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI) – a committee that provides practical and scientific advice to the UK Government.</p> <p>International discussions did not take place, as this was purely a national initiative. From an international perspective, as of 2012, Tyrothricin was available in 10 EU/EEA member states, including the UK.</p> <p>The use of tyrothricin-containing lozenges have been the subject of both academic studies and digital newspaper articles. More specifically, the case has highlighted the need to ensure that the supply of products containing antimicrobials, regardless of legal classification, accurately reflects any clinical guidance updates, therefore remaining clinically relevant.</p> <p>Finally, the case highlights the importance of educating the general public on conditions for which the routine use of antibiotics is inappropriate.</p> <p>The swift action taken in this case reflects the UK Government's commitment to supporting initiatives to tackle AMR and highlighting the responsible use of antibiotics.</p> |

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| | <p>Overall next steps for the MHRA are to continue working collaboratively, play a role in delivering the Government’s 5-year (2019 – 2024) national action plan to tackle AMR and to support the overall UK 20-year vision for AMR. Broadly, the plan focusses on the following three key ways of tackling AMR:</p> <ol style="list-style-type: none"> 1. Reducing need for, and unintentional exposure to, antimicrobials 2. Optimising use of antimicrobials 3. Investing in innovation, supply, and access |
| <p>Infographic and/or web links</p> | <ul style="list-style-type: none"> • <u>The National Institute for Health and Care Excellence guidance on acute sore throat (for healthcare professionals)</u> • <u>NHS sore throat guidance summary (for the public)</u> |

Development and progress of pilot study on reimbursement models

Lead: Public Health Agency of Sweden

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| Theme | Human medicines; economic models |
| Region / Agency | Sweden The Public Health Agency of Sweden (PHAS) |
| Problem / Challenge | <p>Access to effective antibiotics is critical for optimal treatment of bacterial infectious diseases. While the pipeline of new antibiotics is worryingly meagre due to scientific and financial challenges, a handful of new antibiotics aimed at treating one or more of World Health Organisation's (WHO) list of critical pathogens have entered the European market in the last decade. It is generally assumed that after approval companies steadily make their products accessible across Europe. However, this is not the case with new antibiotics since the commercial prospects are small in many countries, in particular those with low resistance levels and well-established antibiotic stewardship policies. Good stewardship policy would be to save new antibiotics as a last resort in order to prevent the development of resistance, encouraging very low use. Sweden is an example of a country that pharmaceutical companies are choosing not to market their new antibiotics in due to their small market size, low levels of resistance, and stewardship policies. Nevertheless, patient access to lifesaving antibiotics is crucial in all countries, even those considered as unattractive markets to pharmaceutical companies. Therefore, there is an obvious societal need for action to address this gap in access to lifesaving antibiotics in Sweden.</p> |
| Solution / Intervention | <p>The government of Sweden commissioned the PHAS in 2018 to develop a pilot project for a novel reimbursement model for antibiotics. PHAS developed a partially delinked model for the pilot based on a minimum annual guaranteed revenue at national level to the pharmaceutical company. In return for this minimum annual guaranteed revenue, the supplier ensures that their antibiotic is readily available (capable of delivering the product to hospitals within 24 hours) and has a security stock located in Sweden.</p> <p>The healthcare system in Sweden is decentralized, and during the pilot study the various regions continue to buy and pay as usual for the new antibiotic included in a national contract during this pilot study. If the revenue from actual sales from the regions is lower than the guaranteed income for a given year, the difference will be paid from the national level at the end of the year to the relevant supplier. If, on the other hand, revenue from actual sales exceeds the guaranteed level for a given year, the company receives an additional 10% of the value of the guaranteed annual compensation for fulfilling the availability requirements.</p> |

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| | <p>The dollar amount of the minimum guaranteed annual revenue is based on a forecast of estimated clinical needs for Sweden over the contract years. For the current pilot, the maximum annual revenue is calculated to approximately 400 000 Euro per drug. Vinnova (the Swedish innovation agency) is the financier for the guaranteed payments.</p> <p>In the design of the pilot, thorough consideration was given to the legislative aspects of the project, including state aid, procurement rules and antitrust laws. To support transparency, as part of the pilot design, eligible pharmaceutical companies were invited to an information meeting to provide input and feedback. Some of the alternative pilot options considered early in the process were national stockpiling and to select only one product under contract for the pilot period, instead of allowing all products that fulfilled the requirements.</p> |
| <p>Results / Accomplishments</p> | <p>The pilot study was initiated in July 2020 and runs through 2022. As of April 2022, the pilot is in the evaluation and monitoring phase and the final report to the Swedish Government is due December 2022. Evaluation and follow-up research will be performed partly in-house by PHAS and partly by contracted external parties.</p> <p>Fulfilment of required specifications, the economic consequences for the health care system and for concerned pharmaceutical companies, (whether or not they are participating in the pilot), and procurement processes will be evaluated. Indicators closely monitored throughout the study period are sales data, expenditure and storage status, time from order to hospital delivery, clinical use and patient outcomes of the contracted antibiotics, and the time from approval by the European Commission to national launch.</p> |
| <p>Learnings / Recommendations</p> | <p>Learning, recommendations and next steps will depend on the outcome of the pilot study evaluation which is underway.</p> |
| <p>Infographic and/or web links</p> | <ul style="list-style-type: none"> • Questions and answers: Agreements signed for a pilot study of a new reimbursement model |

Reporting selective antibiograms

Lead: Swedish Medical Products Agency

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| Theme | Human medicines; diagnostic tests |
| Region / Agency | Sweden Swedish Clinical Microbiology Laboratories; the Swedish Reference Group for Antibiotics (RAF); Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA); the Public Health Agency of Sweden (PHAS); and the Swedish Medical Products Agency (SMPA). |
| Problem / Challenge | Increasing AMR is a global problem driven by antibiotic use in human and animal medicine. Adequate, tailored, specific information about a patient's infection can support clinicians and guide them to the best available antibiotic choice, and towards narrow spectrum antibiotics, if possible, at the time of treatment decision. Selective resistance profile information (antibiograms) is a powerful tool that can enable clinicians to avoid inappropriate antibiotic use, including unnecessary broad-spectrum antibiotic use. |
| Solution / Intervention | <p>The PHAS together with other Swedish regulatory agencies and the local laboratories provide data on resistance levels, and give recommendations on best practices for surveillance and reporting. This allows the most effective and evidence-based substances for each microbe and situation to be tested and reported, instead of every available antibiotic. The local laboratories select what antibiotics to test and include in the antibiogram based on current national, regional, and local AMR data, and in accordance with changes in national treatment guidelines.</p> <p>One illustrative example of specific resistance profile testing guidance, based on infection type and surveillance data, is the guidelines for a urinary culture <i>Enterobacteriaceae</i> antibiogram for patients with symptoms of cystitis (lower urinary tract infection). The antibiograms in Sweden differ in accordance with the patient sex in this case. Six antibiotics are tested and reported in the antibiogram for men, whereas only five of them are reported for women. Ciprofloxacin, a fluoroquinolone, is today included in the antibiogram for men but not for women since it is no longer recommended in the national cystitis treatment guidelines for women. If necessary, the clinician can still call the laboratory to get the test results for ciprofloxacin.</p> |
| Results / Accomplishments | Reflecting the example of selective reporting of fluoroquinolones above, fluoroquinolone prescriptions in Sweden have decreased by 46% in 15 years, from 430 in year 2006 to 233/1000 inhabitants per year in 2020, mainly through the decreased use in treatment of uncomplicated urinary tract infection. |
| Learnings / Recommendations | <p><i>Recommendations</i></p> <ul style="list-style-type: none">• Secure national access to narrow-spectrum antibiotics to enable effective treatment without increasing AMR, whenever possible.• Guide clinicians towards narrow spectrum alternatives whenever appropriate, through the use of selective antibiograms. |

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- Ensure that there are no economic incentives for microbiological laboratories to test and report more than the recommended substances in antibiograms, nor any economic incentives for doctors to prescribe more, longer, or broader spectrum antibiotic treatment.

Next steps / plans for future

- The antibiotic resistance levels for *Enterobacteriaceae* are changing rapidly and decisions on selective antibiograms require continuous vigilance and compliance with local, regional, and national resistance levels.
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Feedback on prescriber data

Lead: Swedish Medical Products Agency

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| Theme | Human medicines |
| Region / Agency | Sweden STRAMA, PHAS, SMPA |
| Problem / Challenge | The need to reduce inappropriate treatment, unnecessary broad or long antibiotic courses and excess use of antimicrobial substances for unspecific reasons is urgent. However, adherence to national and regional AMU guidelines vary significantly among hospitals, clinics, health centers and doctors. |
| Solution / Intervention | <p>Providing prescriber data feedback at the national, regional, local, and even individual level is a powerful and effective way to influence antibiotic prescription habits. Benchmarking through open comparisons of antibiotic use in regions, hospitals and health centers has been used successfully in Sweden for a long time. Individual feedback to doctors through a well-informed trusted source with access to the individual prescriber data, which in Sweden is done via local STRAMA representatives, can provide valuable individual-level pressure to change prescribing habits when appropriate. It is also an opportunity to inform, educate and correct misperceptions.</p> <p>The PHAS provides prescriber data across levels using existing prescriber identifying codes. Governmental authorities communicate differences in national and regional levels, and local STRAMA networks deal with higher resolution (i.e., individual) prescriber data.</p> <p>In order to track prescriber data and communicate relevant trends and feedback across levels of the healthcare system, continuous work is needed to maintain the databases and update the feedback parameters when there are changes in guidelines and recommendations.</p> <p>The local STRAMA networks accomplishes this important work within their existing budgets which vary across the country.</p> |
| Results / Accomplishments | <p><i>Regulatory guidance or changes</i></p> <ul style="list-style-type: none">• Legally ensure access to high resolution prescriber data through the use of prescriber identifying codes. <p><i>Publications / public information</i></p> <ul style="list-style-type: none">• Statistics on antibiotic use at regional and national levels are openly accessible through the National Board of Health and Welfare website, and monthly updated reports are compiled and presented by the PHAS and available on their website. <p><i>Metrics / statistics related to measuring or evaluating the intervention</i></p> <ul style="list-style-type: none">• Prescriber data are easily monitored over time and evaluations show that antibiotic prescriptions have decreased steadily in Sweden for almost |

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| | <p>thirty years, from 560 antibiotic prescriptions per 1000 inhabitants per year in 1992, to 237 per 1000 in 2020.</p> |
| <p>Learnings / Recommendations</p> | <p><i>Role as a regulator</i></p> <ul style="list-style-type: none"> • Continuous collection of high-resolution prescriber data is essential to enable individual feedback and comparisons between units within a given organizational level. <p><i>Next steps / plans for future</i></p> <ul style="list-style-type: none"> • A decision to extend the regulations regarding individual identity codes for prescribers has been made to also include veterinarians, who were previously exempt from this regulation. |
| <p>Infographic and/or web links</p> | <ul style="list-style-type: none"> • The National Board of Health and Welfare statistic database website: Statistikdatabaser - Läkemedelsstatistik - Val (socialstyrelsen.se) • Monthly updated reports on antibiotic use in all Swedish regions: Månadsstatistik till och med oktober 2021 Öppenvårdsförsäljning av antibiotikarecept Riket och alla län (folkhalsomyndigheten.se) |

Treatment recommendations for common infections in outpatient care – the Rainbow Pamphlet

Lead: Swedish Medical Products Agency

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| Theme | Human medicine |
| Region / Agency | Sweden STRAMA, PHAS, SMPA |
| Problem / Challenge | The need to reduce inappropriate or overuse of antibiotics, including antibiotic treatment courses that are unnecessarily broad or long and unspecific excess use of antimicrobial drugs, is urgent. |
| Solution / Intervention | <p>To address this issue, STRAMA provides easily accessible, concise, updated and fulsome information on the treatment of the most common infections in primary care settings. All information is available in the same place, from a trusted source (STRAMA), either as a paper pamphlet (see “Regnbågshäftet – The Rainbow Pamphlet” as PDF in appendix) or as a cellphone application “Strama Nationell”.</p> <p>STRAMA is an advisory board to the PHAS, which together with the SMPA develop and publish antibiotic treatment guidelines. STRAMA was initially established as a nongovernmental organisation with high credibility among Swedish physicians and had been working on treatment guidelines for many years prior to when the first “Rainbow pamphlet” was produced over ten years ago, around 2010. The “Rainbow pamphlet” has been accompanied by intense communication directed towards both healthcare professionals and the public to ensure acceptance and adherence to changed guidelines.</p> <p>To maintain up to date treatment recommendations, ongoing continuous work is needed to implement new knowledge and research developments and to adapt guidelines to changes in local, regional and national antimicrobial resistance patterns and alterations in antibiotic supplies.</p> |
| Results / Accomplishments | <p>By providing updated recommendations on when to use antibiotics, the correct product, dosage and treatment duration to primary care physicians, Swedish family doctors today prescribe an average of 10.3 DDD per 1000 inhabitants per day, as compared to the European average of 18.0 DDD/1000 inhabitants per day.</p> <p>Since 1999, there are two examples of major changes in guidelines and hence prescription habits that have occurred:</p> <ul style="list-style-type: none"> • the pronounced reduction of quinolone usage in lower urinary tract infections in women and more recently also in men, and • the cessation of the use of antibiotics for the treatment of uncomplicated otitis (ear infections/inflammation) media in children between 1 and 12 years of age. <p>Prescriptions in Sweden have also decreased since the inception of these</p> |

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| | <p>recommendations. The number of antibiotic prescriptions per 1000 inhabitants has decreased from a national average of 472 antibiotic prescriptions per 1000 inhabitants in 1999, to 390 prescriptions in 2010, to 237 / 1000 inhabitants in 2020.</p> <p>A national goal of maximum 250 antibiotic prescriptions / 1000 inhabitants (called the 250-goal set in 2009) was reached last year, likely further facilitated by the COVID-19 pandemic.</p> |
| <p>Learnings / Recommendations</p> | <p><i>Role as a regulator</i></p> <ul style="list-style-type: none"> • Access to national, regional, and local data on antimicrobial resistance levels are necessary to enable targeted and evidence-based recommendations <p><i>Next steps / plans for future</i></p> <ul style="list-style-type: none"> • Continuous monitoring for unintended impacts on public health, including potential unwanted side effects of reduced treatment levels, such as increased occurrence of infection related complications, hospitalisations and increased incidence of severe disease and sepsis. Thus far, no such effects have been detected. • Further development of current guidelines in terms of, for example, evidence-based reduction of treatment duration. |
| <p>Infographic and/or web links</p> | <ul style="list-style-type: none"> • The “Rainbow pamphlet – Regnbågshäftet”: Behandlingsrekommendationer för vanliga infektioner i öppenvård (folkhalsomyndigheten.se) |

Developing methods for monitoring AMR in the environment

Lead: Swedish Medical Products Agency

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| Theme | Developing methods for monitoring AMR in the environment |
| Region / Agency | Sweden and international partners Swedish Medical Products Agency (SMPA) with knowledge gained from the research projects EMBARK (Establishing a Monitoring Baseline for Antimicrobial Resistance in Key environments) and SAntibiotikasmart Sverige (Antibiotic smart Sweden) |
| Problem / Challenge | <p>A broad range of interventions within the healthcare sectors have been implemented in Sweden and other countries to curb the development of AMR. Increasingly, there is a growing recognition that a One Health-perspective is needed, encompassing human, veterinary and environmental health when examining practices to reduce AMR. There are large knowledge gaps regarding the abundance and prevalence of antibiotic resistance genes (ARGs) and Mobile Genetic Elements (MGEs) occurring naturally. At the same time, there is an urgent and increasing need to understand the development and transmission of AMR both into and within the environment. Research has shown that antibiotics and other antimicrobials may be emitted into the environment at different points throughout the lifecycle of human and veterinary pharmaceuticals. In addition to antibiotics and antimicrobials, antibiotic resistant bacteria, ARGs and MGEs can, for example, reach water environments via improper treatment of pharmaceutical manufacturing waste streams, direct environmental contamination in aquaculture or plant production, landfill leachates, runoff from agricultural production, human and animal use and excretion, through improper disposal and/or handling of unused drugs, and from sewer overflow events.</p> <p>As the environment can provide a route for some resistant bacteria to colonize or infect hosts (environmental transmission), introducing environmental monitoring of ARGs and antimicrobials is one crucial aspect in understanding routes and hotspots for the spread and occurrence of AMR. Currently there is a lack of agreed upon targets and standardized methods and monitoring programs in water and other environments, partly due to the complexity of AMR warranting a multi-target, adaptable approach. Improved data and surveillance are key to better plan and implement actions and measures to minimize the release of substances with antimicrobial properties into the environment in order to combat the development and spread of AMR from a One Health perspective.</p> |
| Solution / Intervention | A One Health approach promotes harmonised surveillance across human, veterinary and food sectors and the use of common outcome indicators to monitor AMR and AMU. To date, several joint national or international reports publish AMR trends for key indicator bacteria and key antibiotics (e.g. Swedish Surveillance of antibacterial resistance ¹ , WHO Global Antimicrobial Resistance |

and Use Surveillance System GLASS², DANMAP³). However, there is no clear consensus on which indicators to measure for the environmental sector.

Monitoring AMR in the environment could include measures such as:

- Determining sources of AMR in the environment
- Determining where humans are exposed to resistant bacteria from the environment and which forms of AMR is dominant.
 - One step could potentially be to map where humans interact with bacteria from the environment and monitoring is already in place (e.g. bacteria that might develop resistance and are monitored connected with bathing or drinking water).
- Detect changing patterns of resistance over time and allowing for temporary or long-term public health efforts and interventions such as closing beaches or drinking water advisories.
- Developing early warning systems for upcoming AMR threats and enabling implementation of measures to combat them before they become major clinical problems.

To successfully determine adequate and suitable action to combat AMR, we need to monitor and establish a baseline for normal AMR (and ARG) levels in different environments (normal here referring to how many resistance genes are typically found in different environmental compartments and ecosystems, such as an unpolluted lake, in drinking water or soil, in urban environments, etc.). Determining this baseline is a prerequisite for comparing levels and to detect if a monitored environment deviates from normal (i.e., is more polluted).

Currently there are several ongoing and planned projects with Swedish researchers and/or government agencies focusing on establishing baselines and/or monitoring of antibiotic and antimicrobial resistance in the environment. Two examples, *EMBARK* and *AntibiotikaSmart Sverige*, are described in this case study.

EMBARK (Establishing a Monitoring Baseline for Antimicrobial Resistance in Key environments)

EMBARK is an international collaboration project funded by the Joint Programming Initiative on AMR (JPIAMR) in 2019, spanning six research groups in five countries (Sweden, Germany, China, France, Pakistan).

EMBARK takes a One Health approach to understanding and controlling AMR outside of the healthcare setting. The project aims to:

- Establish a baseline for how common resistance is in the environment and what resistance types can be expected where
- Standardize different methods for resistance surveillance and identify high-priority target that should be used for efficient monitoring.

The SMPA are invited stakeholders in *EMBARK*'s Monitoring Framework Group. The *EMBARK* Monitoring Framework Group is currently discussing suitable

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| | <p>methods and protocols for monitoring AMR in the environment. Questions discussed include:</p> <ul style="list-style-type: none"> • How to standardize and compare different methods for environmental monitoring? • Which methods to develop and use to detect emerging resistance threats (e.g. qPCR, (functional) metagenomics)? • How to develop a modular monitoring framework which allows for comparison (and/or integration) of data between agencies and countries and existing data infrastructures? • In which environments to conduct monitoring (e.g. water, soil, sewage, meat and surfaces coupled to for instance industrial pollution and wastewater, bathing and drinking water, agriculture and aquaculture including manure and sludge)? • Which bacteria and types of resistance to include in monitoring efforts? <p><i>AntibiotikaSmart Sverige (Antibiotic Smart Sweden)</i></p> <p>The ongoing project is a Swedish research project funded by Vinnova, Sweden's innovation agency, spanning twelve national organisations. The project works broadly with measures to increase societal knowledge regarding AMR, aiming to develop AMR-smart regions and municipalities that actively combat AMR. The SMPA has been interviewed and given the opportunity to comment on proposed criteria for monitoring AMR in the municipal and sewage sectors.</p> <p><i>AntibiotikaSmart Sverige</i> develops proposals for monitoring criteria for the municipal water and sewage sector, building a knowledge base on where resistant bacteria are found in order to identify areas where measures can be implemented to counteract the spread of antibiotic substances and AMR.</p> <p><i>Nordic Council of Ministers: Nordic AMR One Health Expert Group</i></p> <p>There are currently discussions among member states of the Nordic Council of Ministers Nordic AMR One Health Expert Group regarding seeking funding for a project with the aim of developing a common Nordic strategic approach for environmental AMR monitoring. The SMPA is part of the Expert Group which develops the scope of the potential project.</p> <p>¹ Surveillance of antibacterial resistance - The Public Health Agency of Sweden (folkhalsomyndigheten.se)</p> <p>² https://www.who.int/initiatives/glass</p> <p>³ https://www.danmap.org/</p> |
| Results / Accomplishments | <p>Since <i>EMBARC</i> is ongoing and the <i>AntibiotikaSmart Sverige</i> is in the planning phase, there are no results that have been finalized or published. However, some progress has been published on the respective website (see web links in section below).</p> |
| Learnings / Recommendations | <p>As all the projects are either ongoing or in the planning phase, it is premature to give any recommendations.</p> <p>However, the <i>EMBARC</i> Monitoring Framework Group has discussed the possibility to develop a modular monitoring scheme/strategy that takes into account both monetary resources and legal and practical constraints. Some</p> |

adaptation of techniques, etc., might be necessary depending on if the monitoring is implemented in low-, middle- or high-income countries, while still aiming to make the monitoring relevant and comparable between countries and different situations.

Within the *AntibiotikaSmart Sverige* project, consideration is being given to narrowing the initial focus to monitor antibiotics that have the highest recorded national use based on statistics from STRAMA⁴. To the SMPA's knowledge this has not been decided but might be an aspect to consider in other geographical settings/projects.

⁴<https://janusinfo.se/behandling/stramastockholm/antibiotikastatistikochresistensdat a.4.10adba9e1616f8edbc9ba3a.html>

Understanding that the environment can play an important route for the evolution, transmission, spread and development of AMR between and among humans, animals, food systems and ecosystems is key to develop frameworks for monitoring and surveillance of AMR. Increased and openly available knowledge and data is key to support measures for tracking and mitigating the spread of AMR via the environment. This data is crucial also for informing epidemiological studies and human health risk assessments.

Infographic and/or web links

- [EMBARK](#)
 - [Antibiotikasmart Sverige](#)
 - [Nordic Council of Ministers](#)
-